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OEIS Complex — A Population Study

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Using a novel method for the analysis of infants with multiple malformations, we investigated the cluster of associated malformations called the OEIS (omphalocele, bladder exstrophy, imperforate anus, spine defect) complex among 5,260 infants with multiple malformations identified in four large registers of congenital malformations, corresponding to 5.84 million births. The existence of the OEIS complex was clearly demonstrated and malformations entering it could be defined. Other than the four classical malformations, omphalocele, bladder exstrophy, imperforate anus, and spine malformation, a strong association with spina bifida and intersex was stressed. Spine malformations occurred not only in the lumbosacral level but also more cranially, and an association also with upper spina bifida could be demonstrated. No specific association with any other malformation, including cardiac defects, was apparent. The OEIS complex is an unusually clearly defined entity among the various nonrandom associations which have been described. Am. J. Med. Genet. 92:62–68, 2000.

KEY WORDS: multiple malformations; OEIS complex; omphalocele; bladder exstrophy; anal atresia; spine malformation; intersex

INTRODUCTION

In 1978, an association between four severe congenital malformations was described with the acronym OEIS (omphalocele, bladder exstrophy, imperforate anus, spine defect) [Carey et al., 1978]. Examples of spine malformations included hemivertebrae and sacral meningoceles. The description was based on a search of medical records in one large California hospital identifying 175 infants with one or more of the above-mentioned malformations. Twenty-nine of these infants had two or more of the four "cardinal" defects and six infants exhibited all four defects (the full complex). One of the patients had trisomy 18. To this material was added four infants identified with the full complex from a genetic service. The features of the 10 infants with a full complex were described. Among the 10 infants, genital anomalies were found in six, e.g., absence of external genitalia, ambiguous genitalia, abnormal phallus, epispadias, or bifid scrotum. These were regarded to be secondary features of the complex.

Some previous reports on this constellation have been published under various names, e.g., vesicointestinal fissure or exstrophica splanchnica, as reviewed by Carey et al. [1978]. The constellation has since then repeatedly been described in the literature and is regarded as an entity, probably arising very early during embryonic development [Haldar et al., 1994]. The majority of descriptions are based on clinically identified cases which seem to fulfil the criteria for OEIS.

A strong association between imperforate anus and lumbosacral spine defects is well known. In infants with anal atresia, omphalocele, and bladder/cloacal exstrophy are overrepresented [Harris et al., 1995], and an association between omphalocele, spina bifida, abdominal wall defects, and bladder exstrophy has been described repeatedly [e.g., Källén, 1987a].

We have tried to identify and characterize the OEIS complex from an unbiased dataset of infants with multiple malformations. A substantial part of the data in

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two previous studies [Källén 1987a,b; Mastroiacovo, 1991] is included in the present analysis. We avoided the use of the terms "developmental field," "primary field," or "blastogenetic origin." We feel that such terms express ideas about pathogenesis which are not addressed by epidemiological methods. We refer the reader to Opitz [1993].

MATERIALS AND METHODS

Data were obtained from four well-established malformation monitoring programs (Central-East France, Italy: IPIMC; South America: ECLAMC; and Sweden: RCM), and were collected as case records according to an agreed-upon record lay-out. For each infant with at least two of 73 selected malformations, the following information was given: presence or absence of each one of the 73 malformations, program, gender, maternal age, stillbirth, and autopsy. A table of the included malformations and a description of the participating programs have been published previously [Källén et al., 1999a]. Data were drawn from a total of 5.84 million births and 5,260 infants with multiple malformations were analyzed.

In order to make an unprejudiced investigation of the OEIS complex, a procedure was performed which was previously used in a study of the CHARGE association and which was described in detail in previously [Källén et al., 1999a,b].

Possible associations between malformations (and pairs of malformations) were investigated using multiple logistic regression analyses. For each malformation or (malformation combination) an analysis was performed with the particular malformation as the outcome variable, and odds ratios (ORs) for other malformations were calculated, adjusted for possible confounders such as program, gender, maternal age, stillbirth, autopsy, and number of malformations [Källén et al., 1999a]. If necessary, a forward selection was used to select the most important confounder(s) so that the number of independent variables never exceeded 1/10 of the number of cases (infants with the outcome variable).

In a first step, pairwise associations between the selected 73 malformations were identified (first-hand associations), in a second step supplemented with second-hand associations, hidden in the first step by other strong associations. Next, associations found between pairs (first-hand or second-hand) and a third malformation were identified ("triplets"). Such an association between a pair of malformations (A and B) and a third malformation (C) was considered significant only if malformation C was significantly present more often when A and B were simultaneously present than when malformation A or B was alone.

Criteria for an individual infant to belong to the OEIS constellation were decided on the following principles previously described [Källén et al., 1999b]. The method can briefly be described as follows: For each malformation and pair of malformations, the probability was calculated that a third malformation (if present) was within the OEIS group. Infants with pairwise malformation combinations for which those probabilities exceeded 0.60, and infants with three or more malformations within the OEIS spectrum, were selected as probable OEIS cases. Malformations associated with OEIS cases according to this definition were identified by multiple logistic regression analysis. If a strong association between a certain malformation and the OEIS group appeared, the OEIS group (after a thorough investigation) could be expanded to include this particular malformation.

RESULTS

After the introductory analyses, a convincing cluster appeared consisting of spina bifida, anal atresia, omphalocele, bladder exstrophy, intersex, and costo-vertebral malformations. Table I shows the numbers and the magnitude of all significant associations between the individual or pairs of malformations mentioned. As shown in Table I, the number of significant associations between pairs or triplets among the six malformations is impressive.

Costo-vertebral defects were divided according to the level of the defect. Lower (lumbar or sacrococcygeal) vertebral defects were strongly associated with anal atresia, whereas for upper (cervical or thoracic) costo-vertebral defects, two second-hand associations were found (with anal atresia and bladder exstrophy, respectively). Except for the association with anal atresia, all costo-vertebral malformations were associated with intersex and omphalocele, without any predilection for a specific level of the vertebral defect. The results indicate that the costo-vertebral malformations in the OEIS complex involve both upper and lower vertebral defects, and for further analyses no division according to the level of the vertebral defect was made.

In order to select a group of OEIS (the selected group described above) cases, criteria for an individual infant to belong to the OEIS complex were defined. From the dataset, 74 infants with three or more of the six selected malformations and 86 infants with any of nine specific pairs of combinations (Table II) were chosen and regarded as possible OEIS cases. Among the 160 possible OEIS cases, 97 cases had at least one other malformation besides the OEIS-defining malformations. Associations between OEIS and all other possible malformations were looked for, and four malformations which occurred more frequently ($P < 0.05$) than expected among the possible OEIS cases compared to other infants with multiple malformations were found. Those malformations/anomalies are: colonic atresia (OR: 12.9, 95% CI: 4.6–35.8), other body wall defects (OR: 14.8, 95% CI: 7.4–29.6, see Discussion), horseshoe kidney (OR: 5.1, 95% CI: 2.5–10.6), and mullerian duct defects (OR: 6.6, 95% CI: 2.1–20.6). In order to investigate whether these malformations are true components of the OEIS complex, associations between these malformations and all possible pairs were searched for. Table III shows the numbers and the magnitude of all significant associations between the individual or pairs of the selected malformations (only results not shown in Table I).

TABLE I. Results From the Introductory Analyses Which Led to the Selection of the Malformations*

Malformation C Malformation B or malformations A + B	OR (95% CI)	Numbers of infants with both (or all three) malformations
Spina bifida (n = 250)		
Omphalocele	3.0 (2.1–4.2)	46
Anal atresia	1.6 (1.1–2.4)[a]	36
Bladder exstrophy	5.7 (2.8–11.5)	12
Intersex	2.0 (1.2–3.4)[a]	19
Anal atresia and omphalocele (n = 51)	8.2 (4.3–15.6)	15
Omphalocele and bladder exstrophy (n = 18)	29.1 (11.4–74.5)	10
Omphalocele and intersex (n = 27)	10.9 (4.8–24.8)	9
Anal atresia (n = 713)		
Bladder exstrophy	4.1 (2.2–7.6)	23
Omphalocele	1.8 (1.3–2.5)[a]	60
Intersex	4.8 (3.5–6.6)	93
Costo-vertebral defects, total (n = 718)	1.6 (1.3–2.0)	168
Cervico-thoracic (n = 467)	4.8 (3.5–6.6)[a]	90
Lumbo-sacrococcygeal (n = 192)	4.2 (3.0–5.7)	84
Both levels (n = 83)	3.2 (2.0–5.1)	33
Spina bifida and omphalocele (n = 38)	3.1 (1.6–6.3)	15
Omphalocele and intersex (n = 27)	29.6 (11.7–74.8)	21
Bladder exstrophy and intersex (n = 10)	65.6 (8.3–18.5)	9
Intersex and costo-vertebral malf. (n = 34)	13.1 (6.4–27.2)	21
Omphalocele (n = 328)		
Bladder exstrophy	10.9 (5.8–20.5)	20
Intersex	1.6 (1.0–2.5)	29
Spina bifida and anal atresia (n = 32)	12.7 (6.2–26.0)	15
Spina bifida and bladder exstrophy (n = 12)	86.4 (18.4–96.5)	10
Spina bifida and intersex (n = 17)	19.6 (7.5–51.2)	9
Anal atresia and intersex (n = 86)	3.4 (2.0–5.9)	21
Bladder exstrophy (n = 47)		
Intersex	4.5 (2.2–9.3)	11
Lumbo-sacrococcygeal vertebral defect	4.3 (1.6–11.5)	5
Spina bifida and anal atresia (n = 32)	57.0 (19.6–65.6)	6
Spina bifida and omphalocele (n = 38)	67.7 (27.2–68.7)	10
Anal atresia and omphalocele (n = 51)	28.9 (49.0–38.9)	11
Anal atresia and intersex (n = 86)	30.2 (11.4–80.2)	9
Omphalocele and intersex (n = 27)	60.9 (19.5–90.2)	5
Intersex (n = 203)		
Spina bifida and anal atresia (n = 32)	12.8 (5.6–29.1)	10
Spina bifida and omphalocele (n = 38)	4.3 (1.9–10.0)	9
Anal atresia and omphalocele (n = 51)	21.5 (11.5–40.1)	21
Anal atresia and bladder exstrophy (n = 32)	36.8 (14.6–92.4)	9
Omphalocele and costo-vertebral malformations (n = 35)	5.3 (2.2–12.6)	8
Costo-vertebral malformations, total (n = 718)		
Omphalocele and intersex (n = 27)	3.3 (1.4–7.7)	8

*Associations between malformation C and B, or between malformation C and the pair A + B. Odds ratios with 95% CI adjusted for the most important confounders selected from: program, year of birth, maternal age, gender, stillbirth, autopsy, and number of malformations.
[a]Association found when first-hand associations were removed.

The results from Table I and III are summarized and interpreted in Figure 1. The order of the malformations around the circle of the figure is arbitrary and of no significance. Associations between the involved malformations are symbolized by lines of different types, e.g., the thin, unbroken line between spina bifida and omphalocele represents the significant association between those malformations. The three heavy lines originating from this line shows identified "triplets"; infants suffering from both spina bifida and omphalocele are, compared to infants with one of these malformations only, at increased risk of bladder extrophy, anal atresia, and intersex. Between spina bifida and anal atresia, no significant association was found, and in Figure 1 the line between spina bifida and anal atresia is dotted. However, if spina bifida and anal atresia are present simultaneously, strong associations with bladder extrophy, omphalocele, and intersex were found. Those associations are symbolized in Figure 1 as heavy lines originating from the dotted line between spina bifida and anal atresia. Between spina bifida and intersex, no significant association was found until other strong ("first hand") associations were removed. This "second hand" association is symbolized by a dashed line. The heavy lines originating from this dashed line shows that infants with intersex and spina bifida are at significantly increased risk of omphalocele or bladder extrophy.

The figure shows the impressive number of associations between the malformations involved and sug-

TABLE II. Pairwise Combinations of Malformations Within the OEIS Spectrum Defined After the Introductory Analyses Which Qualify an Individual Infant to Belong to the OEIS Constellation (Preliminary Group)*

Combination	Numbers with one more malformation	Numbers with one more malformation within OEIS	Percentage with one more malformation within OEIS
Spina bifida + anal atresia	32	24	75
Spina bifida + omphalocele	38	24	63
Spina bifida + bladder exstrophy	12	12	100
Spina bifida + intersex	17	14	82
Anal atresia + omphalocele	51	35	69
Anal atresia + bladder exstrophy	19	18	95
Omphalocele + bladder exstrophy	18	18	100
Omphalocele + intersex	27	26	96
Bladder exstrophy + intersex	10	9	90
Bladder exstrophy + costo-vertebral malformation	34	24	71
Intersex + costo-vertebral malformation	34	24	71

*A certain pairwise combination was regarded to qualify if the estimated probability exceeded 60% for an infant with at least two malformations within the OEIS to also have a third malformation within this group.

gests that the preliminary OEIS group could be expanded to include colonic atresia, other body wall defects, and mullerian duct defects. The results suggest that horseshoe kidney is not a part of the association. Instead, horseshoe kidney, spina bifida, and omphalocele seem to form an entity of its own.

New criteria for an individual infant to belong to the OEIS (definite) complex were defined. Table IV shows the estimated probabilities for infants with at least two malformations within the OEIS spectrum to also have a third malformation within this group. Such probabilities will estimate the probability for an individual with those two malformations and no further OEIS malformation to actually represent an (incomplete) OEIS.

Using the inclusion criteria above, 194 probable OEIS cases could be selected from the present dataset (96 had three or more OEIS malformations and 98 had pairs of malformations with probabilities to represent OEIS exceeding 60%). Table V shows the number of OEIS malformations among the 194 cases.

Associations between the definite OEIS complex and

TABLE III. Significant Associations ($P < 0.05$) Between the Malformations*

Malformation C Malformation B or malformations A + B	OR (95% CI)	Numbers of infants with both (or all three) malformations
Spina bifida (n = 250)		
Other body wall defects (n = 53)	2.6 (1.2–5.4)	9
Horseshoe kidney (n = 101)	2.8 (1.5–5.2)	14
Intersex and other body wall defects (n = 16)	9.6 (3.3–27.9)	5
Anal atresia (n = 713)		
Other body wall defects (n = 53)	3.1 (1.6–5.8)[a]	15
Mullerian duct defects (n = 67)	2.8 (1.5–5.4)[a]	19
Costo-vertebral malformations and other body wall defects (n = 16)	5.7 (2.1–15.5)	7
Omphalocele (n = 328)		
Colon atresia (n = 32)	4.2 (1.8–9.9)	8
Horseshoe kidney (n = 101)	1.9 (1.1–3.5)[a]	14
Spina bifida and horseshoe kidney (n = 12)	12.2 (3.8–38.6)	5
Bladder exstrophy (n = 47)		
Colon atresia (n = 32)	11.4 (3.9–33.4)	5
Mullerian duct defects (n = 67)	4.2 (1.2–14.9)	4
Intersex (n = 203)		
Other body wall defects (n = 53)	5.6 (2.9–11.1)	16
Anal atresia and other body wall defects (n = 15)	49.4 (17.6–138.8)	8
Costo-vertebral malformations and other body wall defects (n = 16)	21.1 (7.8–57.4)	7
Costo-vertebral malformations (n = 718)		
Other body wall defects (n = 53)	2.2 (1.2–4.2)	17
Colon atresia (n = 32)		
Mullerian duct defects (n = 67)	3.9 (1.1–14.2)	4
Other body wall defects (n = 53)		
Mullerian duct defects (n = 67)	6.2 (1.4–26.9)	4
Spina bifida and intersex (n = 17)	60.5 (20.2–181.4)	5
Intersex and costo-vertebral malformations (n = 34)	24.5 (9.1–66.3)	7

*Only results which are not already shown in Table I.
[a]Association found when first-hand associations were removed.

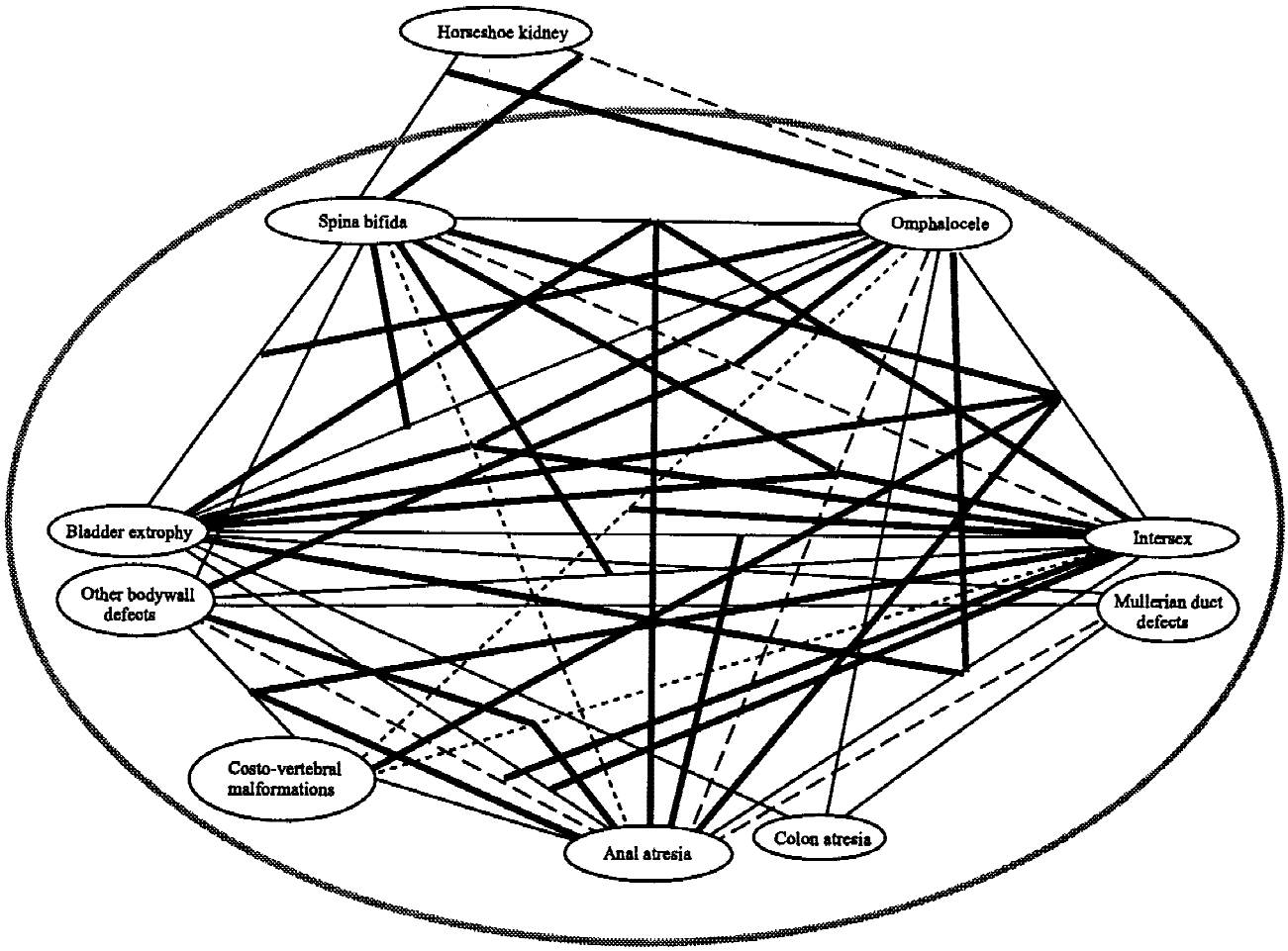

Fig. 1. Visualization and summary of Tables I and III. Thin unbroken lines show significant ($P < 0.05$) associations and dashed lines show associations found when first-hand associations were removed. Heavy, unbroken lines show significant associations between a third malformation and pairs in which the involved malformations may be associated (thin lines or dashed lines as above) or not (dotted lines).

all other possible malformations were looked for, but no further significant associations were found.

DISCUSSION

The methodology used in this article, based on a previous report [Källén et al., 1999a], refines the analyses of infants with multiple malformations, trying to identify nonrandom associations between specific malformations. The analysis was made in successive steps.

In the first step, a number of groups of malformations seemingly associated with each other were identified. One such group obviously contained infants who fulfill the criteria of the OEIS complex. In the

TABLE IV. Estimated Probabilities for Infants With at Least Two Malformations Within the OEIS Spectrum to Also Have a Third Malformation Within This Group*

	Spina bifida	Anal atresia	Omphalocele	Bladder extrophy	Intersex	Costovert. def.	Colon atresia	Other BW def.
Spina bifida	—							
Anal atresia	24/32 (75%)	—						
Omphalocele	26/38 (68%)	35/51 (69%)	—					
Bladder extrophy	12/12 (100%)	18/19 (95%)	18/18 (100%)	—				
Intersex	15/17 (88%)	45/86 (52%)	26/27 (96%)	10/10 (100%)	—			
Costo-vert. def.		38/131 (29%)	15/35 (43%)	7/7 (100%)	27/34 (79%)	—		
Colon atresia	3/3 (100%)	4/5 (80%)	4/7 (57%)		2/2 (100%)	2/3 (67%)	—	
Other BW-def.	6/7 (86%)	13/15 (87%)	2/2 (100%)	3/3 (100%)	14/16 (88%)	12/16 (75%)	1/1 (100%)	—
Mullerian duct	3/4 (75%)	7/12 (58%)	6/8 (75%)	4/4 (100%)		7/12 (58%)	3/4 (75%)	3/4 (75%)

*BW = body wall, def = defect. For each pair of malformations as specified, the number of infants with one more malformation within the OEIS spectrum, the number of infants with at least one more malformation, and the proportion between these two groups are shown.

TABLE V. Number of Malformations Involved in the OEIS Complex Among 194 Infants Regarded as Probable OEIS Cases*

Malformation	Number	OR (95% CI)
Spina bifida, total	77	16.6 (11.8–23.2)
Upper	7	2.9 (1.3–6.7)
Lower	57	19.1 (13.1–28.1)
Anal atresia	118	13.4 (9.8–18.3)
Omphalocele	102	21.9 (15.8–30.3)
Bladder exstrophy	35	139.9 (67.9–288.0)
Intersex	73	20.0 (13.9–28.7)
Costo-vertebral malformations, total	60	3.2 (2.3–4.5)
Cervico-thoracic	24	1.7 (1.1–2.6)
Lumbo-sacrococcygeal	21	5.1 (3.1–8.4)
Both levels	9	5.1 (2.5–10.7)
Colonic atresia	11	19.3 (8.8–42.2)
Other body wall defects	34	44.5 (24.1–82.3)
Mullerian duct defects	18	15.0 (7.5–30.1)

*For each of the listed malformations, an OR is shown for an OEIS infant to have that malformation compared with other multimalformed infants.

next step, a delimitation of this group was made, adding further malformations which also seem to be related to the OEIS group.

The primary cluster of malformations contains the four classical OEIS malformations: omphalocele, bladder exstrophy, imperforate anus, and spine (costo-vertebral) defect. To this spina bifida was added. In the OEIS acronym, S stands for spine (costo-vertebral) defects but in the very first description of infants with OEIS [Carey et al., 1978], the presence of sacral meningoceles is mentioned.

In a detailed study by Pang [1993] based on 34 individuals referred to neurological examination because of sacral agenesis, four were identified as having OEIS with omphalocele, cloacal exstrophy, imperforate anus, and subtotal sacral agenesis. All also had ambiguous external genital organs, and three had lumbar myelocystocele.

Our study, however, showed that costo-vertebral defects were not limited to caudal levels (lumbar or sacral) but that there is an association also with further cranial, even cervical, defects. Similarly, the association with spina bifida is not limited to caudal levels but an association is also seen (although weaker) with upper spina bifida. The complex thus seems not to be exclusively restricted to the caudal end of the body, as suggested by the pathogenetic discussion carried out by Pang [1993], concentrating on errors in the development of secondary neurulation in the caudal end of the body. Pang's material was, however, defined by the presence of a caudal defect: sacral agenesis.

The primary identification of the complex in our analysis included bladder exstrophy. Scrutiny of these records showed that some could perhaps have been classified as cloacal exstrophy. Also, among the cases reported by Pang [1993] cloacal exstrophy was mentioned. These two conditions are closely related (see discussion by Pang, p 771–772) and from the available information were sometimes difficult to distinguish from each other.

Four further malformations were heavily associated with the OEIS complex: "other body wall defects," colonic atresia, intersex, and mullerian duct defects. The term "other body wall defects" means defects which have not been classified as omphalocele or gastroschisis. We scrutinized the records of these 34 cases. The majority represented large body wall defects of the type seen, for instance, in body stalk agenesis, but in a very few cases the distinction from large ruptured omphalocele or gastroschisis was not clear.

Colonic atresia is closely related to anorectal atresia, and also to cloacal exstrophy and the association found was expected.

The similarities are striking between the nonrandom association of malformations described in the present article and the "cloacal exstrophy type" cluster described by Mastroiacovo [1991]. However, as mentioned in Materials and Methods, a substantial part of the data in that study is included in the present analysis. Intersex/ambiguous genitalia and mullerian defects have been repeatedly described in the clinical literature on the OEIS complex [e.g., Carey et al., 1978; Pang, 1993]. The very strong association of intersex in the complex may indicate placing an extra I in the acronym: OEIIS.

In some case reports, the presence of a cardiac defect is mentioned [e.g., Kant et al., 1997]. We found no evidence for a specific association between infants with the OEIS complex and cardiac defects—they were not more common than in other infants with multiple malformations.

As seen in Figure 1, one further malformation is weakly associated with the complex: horseshoe kidney. This association is, however, restricted to the triad spina bifida—horseshoe kidney—omphalocele and seems to have nothing to do with the well-established association among the malformations in the OEIS complex. These cases may well represent unidentified trisomy 18 infants, as these three malformations are common in that condition. It has been shown that the increasing rate of registered trisomy 18 in Sweden may be explainable by an increasing identification of this chromosome anomaly among infants with multiple malformations [Pradat and Robert, 1991], and some may still go unidentified both in this and in the other programs.

The present analysis has also amply verified the existence in an unbiased analysis of a clinically recog-

nized nonrandom association. Its delimitation is unusually clear-cut compared with what is seen in analyses of some other such nonrandom associations, e.g., the caudal deficiency and VATER [e.g., Källén, 1987b] constellations, which appear more as part of more complex families of associations. Also, our analysis of the CHARGE association [Källén et al., 1999b] resulted in a much less clearly defined group of associated malformations. Nevertheless, the OEIS complex appears not to be so strongly restricted to the caudal part of the body as is sometimes thought, but the error in morphogenesis resulting in OEIS may also involve further cranial parts of the body.

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